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Effect of Perchlorate on the Human Thyroid Gland

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A FUNDAMENTAL property of the thyroid gland is that of removing iodide from the perfusing blood and concentrating it in the processes of hormone synthesis and storage. During recent years a large number of substances have been found that interfere specifically with either iodide capture (trapping) or hormone synthesis. Among those preventing the latter are clinically important drugs such as propylthiouracil and 1-methyl-2-mercaptoimidazole. These prevent the oxidation of iodide ion to iodine and its chemical attachment to tyrosyl groups. It remains in doubt whether this occurs through inhibition of an oxidative enzyme, or from maintenance of the trapped iodide ion in the reduced state, or through some other mechanism. It is evident, however, that thiourea and related substances do not prevent the *trapping* of iodide by the gland.[1]

The trapped iodide exists in dynamic equilibrium with the iodide ion of the blood. If the trapped iodide is labeled with I^{131} it can be rapidly diluted out by the administration of a relatively large amount of the stable isotope, I^{127}. The administration of thiocyanate ion, an ion sharing many properties in common with iodide, will also result in a discharge of trapped iodide from the gland. Likewise, prior treatment with thiocyanate will prevent the accumulation of I^{131}.

In a systematic survey of anions that might have an effect similar to that of thiocyanate, Wyngaarden, Wright and Ways[2] found that in the rat perchlorate was approximately 10 times as effective as thiocyanate. I^{131} accumulated by the thyroid of the rat receiving propylthiouracil was rapidly discharged when perchlorate was injected, and pretreatment with perchlorate effectively prevented thyroidal accumulation of iodide. The mechanism of action of perchlorate is unknown, but competition for receptor groups of the gland that are responsible for the initial inorganic binding or inhibitory effects on enzyme systems have been suggested.[2, 3]

Perchlorate appears to have had little pharmacological attention. Kahane[4] observed the effects of intravenous injections on four rabbits; 250 mg. of $NaClO_4$ was without effect, but 500 mg. by intracardiac injection caused a transient paralysis of the hind limbs, and in two animals diarrhea. Eichen[5] found the effect of perchlorate on the frog heart to be identical with that of thiocyanate. He administered 1 to 2 gm. orally to patients and observed no ill-effects. Seventy per cent was recovered in the urine in 12 hours and 85% to 90% in 24 hours.

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Durand[6] gave a patient 784 mg. of $NaClO_4$ and found it in the urine 15 minutes later. At three hours 30% had appeared in the urine. He found no evidence of methemogoblin formation.

The similarity of action of perchlorate on the thyroid of the rat to that of thiocyanate suggested an extension of these observations to the human subject. The results herein reported indicate that the effects in thyrotoxic patients are similar.

Methods

The subjects of this investigation were patients with Graves' disease who were attending the Thyroid Clinic of the Massachusetts General Hospital. In almost all there had been no recent treatment for the disease, but an occasional patient had been receiving 1-methyl-2-mercaptoimidazole for a variable period of time. The initial observations were always made at least a month after discontinuance of all therapy.

The antithyroid drug employed was 1-methyl-2-mercaptoimidazole, given orally in a single 30-mg. dose. Tracer doses of I^{131} of approximately 10 microcuries were used. Measurements for the most part were obtained with a lead-shielded scintillation counter employing a sodium iodide crystal.[7] The crystal was approximately 10 cm. from the anterior surface of the neck, and the lead shielding was in contact with the neck. The sensitivity of the machine was approximately 4000 counts per microcurie at the same distance. Counting rates from the anterior part of the thigh were obtained at the same time. The observations on the first four patients were obtained with a four-quadrant scintillation counter.[7] The sensitivity of this device was approximately 1000 counts per microcurie at the geometrical center of the array. The findings with the two devices were in all respects comparable. Forty-eight hour I^{131} accumulations by the glands were obtained from the four-counter array by comparing the patients with a suitable standard and employing a predetermined correction factor. When appreciable radioactivity was present in the neck at the time of a second tracer, a larger tracer was given so as to minimize the background correction.

A series of observations was made on 12 patients with typical Graves' disease. The experiments were of three types. In one the subjects received a blocking dose of 1-methyl-2-mercaptoimidazole, then a tracer of I^{131}, and, when this had accumulated in the gland, an oral dose of $KClO_4$. In the second series the $KClO_4$ was given before the tracer. In the third group the blocking drug was omitted and the $KClO_4$ given prior to the tracer.

Results

Perchlorate Discharge of Accumulated Iodide

To eight patients 30 mg. of 1-methyl-2-mercaptoimidazole was given orally, and to a ninth a dose of 200 mg. of propylthiouracil was administered. Approximately one hour later a tracer of I^{131} was given. The accumulation of this in the neck was recorded at frequent intervals until it was leveling off or slowly declining. At this point quantities of $KClO_4$ varying from 3 to 500 mg. were given orally in small volumes of water. In each patient, except the propylthiouracil-treated patient, there was a sharp fall in the counting rate within a few minutes

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after ingestion of $KClO_4$. This always occurred within 30 minutes. With smaller doses the discharge of the I^{131} was incomplete, but doses of 100 mg. caused a fall in counting rates nearly to, or in one case slightly below, the counting rates

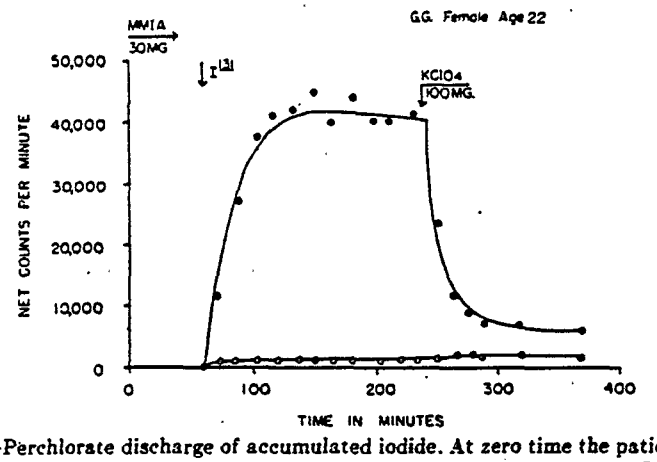

FIG. 1.—Perchlorate discharge of accumulated iodide. At zero time the patient received 30 mg. of 1-methyl-2-mercaptoimidazole. At the first signal, a tracer dose of I^{131} was given and at the second signal 100 mg. of $KClO_4$. The upper curve is counts recorded from the thyroid and the lower those recorded from the thigh. The abscissa is time in minutes; the ordinate is net counts per minute.

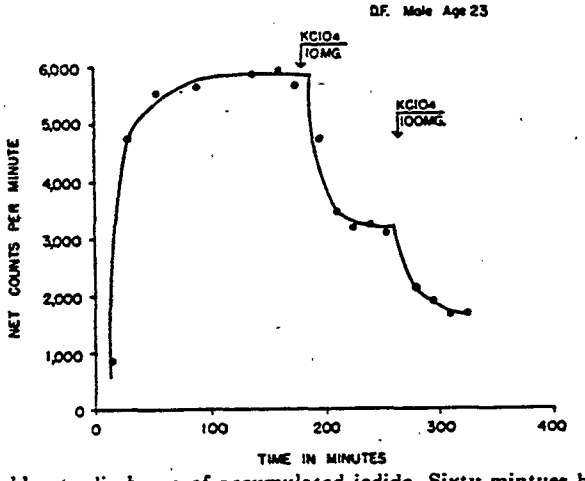

FIG. 2.—Perchlorate discharge of accumulated iodide. Sixty mintues before zero time the patient received 30 mg. of 1-methyl-2-mercaptoimidazole, and at zero time a tracer dose of I^{131}. At the first signal the patient received 10 mg. of $KClO_4$ and at the second signal 100 mg. The abscissa is time in minutes; the ordinate is net counts per minute.

recorded from the thigh. The single instance in which a fall did not occur was in the patient who received propylthiouracil as the blocking agent. The perchlorate was given while the counting rate was increasing. No further increase occurred, and 1 gm. of potassium iodide given orally in solution also failed to cause a fall in counting rate.

Figure 1 illustrates the effect of a single 100-mg. dose of $KClO_4$ on trapped iodide. Only 15% of the initially accumulated I^{131} was present in the neck within a few minutes after administration of the $KClO_4$. At least part of the residual labeled iodide recorded from the neck was in the blood circulating through the structures of the neck rather than in the gland parenchyma. If as a correction the counting rate recorded over the thigh is subtracted, then it appears that scarcely any I^{131} remained trapped within the thyroid after the perchlorate. In Figure 2 is shown the effect of 10 mg. of $KClO_4$ followed by 100 mg. The

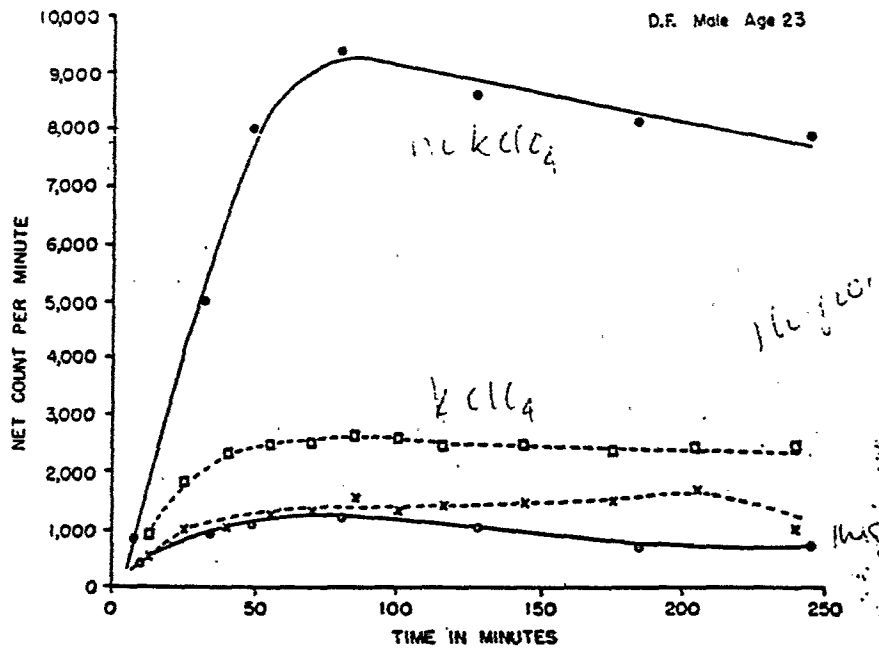

FIG. 3.—Perchlorate inhibition of iodide trapping. One hundred and twenty minutes before zero time the patient received 30 mg. of 1-methyl-2-merceptoimidazole, and at zero time a tracer dose of I^{131}. The solid curves represent the events when the patient received no $KClO_4$. The dashed curves represent the events when 100 mg. of $KClO_4$ was administered 60 minutes before zero time. In each case the upper curve is counts from the thyroid region and the lower curves counts from the thigh. The abscissa is time in minutes; the ordinate is net counts per minute. The two tracers were adjusted to the same counting rate. Note the inhibition of iodide uptake by the prior administration of $KClO_4$.

smaller dose resulted in an incomplete discharge of the I^{131} and the larger dose in a further discharge. The final counting rate over the gland was approximately four times that from the thigh.

Perchlorate Inhibition of I^{131} Accumulation in the Blocked Gland

Two patients received 30 mg. of 1-methyl-2-mercaptoimidazole, and an hour later 100 mg. of $KClO_4$ orally. One hour later tracers of I^{131} were given. A few days later exactly the same observations were made except that the $KClO_4$ was omitted. $KClO_4$ inhibited the accumulation of I^{131} by the thyroid. This is illus-

trated in Figure 3. The patient was a young man with severe thyrotoxicosis. The accumulation of I^{131} in his thyroid when he was pretreated with perchlorate was only 27% of what it was when no perchlorate was given. At least a portion of the I^{131} must have been in the blood of his large and vascular gland rather than in the parenchyma of the gland. When the correction from counting rates over the thigh is made, this value becomes 13%. In the second patient the difference was even more striking. The counting rates from the neck were the same as those from the thigh after administration of $KClO_4$.

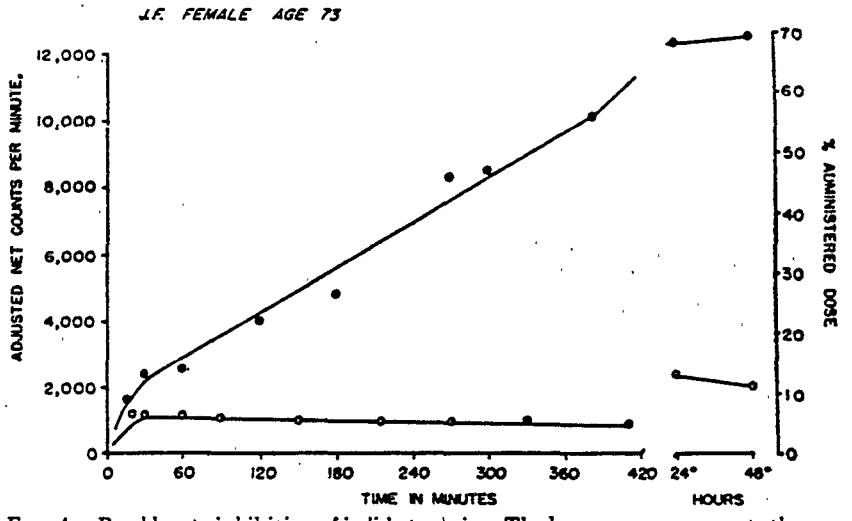

FIG. 4.—Perchlorate inhibition of iodide trapping. The lower curve represents the events when 100 mg. of $KClO_4$ was administered orally one hour prior to zero time. The upper curve was obtained without prior administration of $KClO_4$. The tracers were given at zero time and were adjusted to the same counting rate. The abscissa is time in minutes; the ordinate is counts per minute, or percentage of administered dose in the thyroid.

Perchlorate Inhibition in the Unblocked Gland

Three patients received tracers of I^{131} an hour after being given 100 mg. of $KClO_4$. No 1-methyl-2-mercaptoimidazole was given. Several days later each patient received a control tracer of I^{131} without previous perchlorate. In two, the studies were continued for 48 hours, but in the third a period of observation of only five hours was possible after the tracer.

The single dose of $KClO_4$ strikingly depressed the accumulation rate of the I^{131}, as well as the 24-hour and 48-hour accumulations by the glands. It was apparent in the two longer experiments that after five or six hours there was an inflection in the counting rate curve in an upward direction. This is illustrated in Figure 4. In this patient the 24-hour and 48-hour uptakes of I^{131} were 12.9% and 11.2%, respectively, of the administered dose when they were pretreated with perchlorate, and 68.0% and 69.2% at 24 hours and 48 hours, respectively, when the uptake studies were done without prior administration of perchlorate. In the second patient the control values were 70.3% and 69.9% of the administered tracer dose present in the gland at 24 and 48 hours; when the patient was

pretreated with $KClO_4$, counting rates corresponding to 21.3% and 21.0% were recorded over the thyroid at 24 and 48 hours, respectively.

Discussion

The antithyroid drugs of the thiourea group have provided a means for separating for study the systems of the thyroid involved in iodide trapping on the one hand and hormone synthesis and release on the other. The *iodide of the thyroid* exists in exchangeable equilibrium with the *iodide of the blood*, although there is a considerable concentration gradient in favor of the gland. This iodide has been shown to be nonprecipitable and diffusible.[1] When this space is demarcated with I^{131}, the isotope can be readily diluted out by an excess of I^{127}, and also displaced by an excess of thiocyanate. The latter effect is particularly interesting because a concentration gradient of thiocyanate has not been found.[3] One theory proposed[2] is that these ions are in competition for binding sites on the surface of or within the thyroid cell.

Perchlorate appears to be another substance that can displace iodide from its position in the thyroid gland. The data here presented demonstrate that this occurs with considerable efficiency. A dose as small as 3 mg. given orally produced a considerable fall in thyroidal iodide. Not only is trapped iodide discharged from the glands of patients being treated with the antithyroid drug 1-methyl-2-mercaptoimidazole, but also, if perchlorate is given before the tracer of I^{131}, accumulation of the isotope is inhibited. Perchlorate ion appears, therefore, to have an effect on the thyroid qualitatively similar to that of thiocyanate ion. These data, however, provide no clue to the precise nature of the trapping mechanism or the nature of the effects of perchlorate, or thiocyanate. The similarity of the effects of the two drugs may be only superficial.

The duration of the inhibition of iodide uptake after the oral administration of 100 mg. of perchlorate appeared to be about six hours. Beyond six hours accumulation of I^{131} commenced. Durand[4] found that at this time approximately half the administered dose of perchlorate has been excreted in the urine. A larger dose should provide a more prolonged period of inhibition.

The demonstration of perchlorate goiter in rats by Wyngaarden, Wright and Ways[5] and their demonstration of several other simple substances that inhibit iodide uptake suggest that a variety of hitherto unsuspected agents may be operative in the induction of sporadic goiter. The data here presented on human subjects suggest that perchlorate may have a role in therapeutics.

Summary

Aqueous potassium perchlorate, when given in oral doses of 3 to 100 mg., results in a rapid release of previously accumulated iodide from the thyroid glands of human thyrotoxic subjects treated with 1-methyl-2-mercaptoimidazole. Perchlorate also effectively inhibits the accumulation of tracer I^{131}. This action is qualitatively similar to that of thiocyanate.

The period of inhibition of uptake of I^{131} after a single dose of 100 mg. of perchlorate is approximately six hours.

No toxic effects of perchlorate were encountered in these patients, who were given no more than three doses for a total of not more than 600 mg. of the drug.

REFERENCES

1. VANDERLAAN, J. E., AND VANDERLAAN, W. P.: The iodide concentrating mechanism of the rat thyroid and its inhibition by thiocyanate. Endocrinology *40:* 403, 1947.
2. WYNGAARDEN, J. B., WRIGHT, B., AND WAYS, P.: The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland, Endocrinology *50:* 537, 1952.
3. STANBURY, J. B.: Algunas consideraciones sobre la fisiologia de la glandula tiroides, Revista méd. Chile *79:* 553, 1951.
4. KAHANE, E.: Note sur la toxicite des perchlerates, Bull. Soc. chim. biol. *18:* 352, 1936.
5. EICHEN, O.: Zur Pharmakologie der Perchloratwirkung, Arch. exper. Path. u. Pharmakol. *144:* 251, 1929.
6. DURAND, J.: "Recherches sur l'elimination des perchlorates. sur leur repartition dans les organes et sur leur toxicite, Bull. Soc. chim. biol. *20:* 423, 1938.
7. BROWNELL, G. L., AND STANBURY, J. B.: Instrumentation for thyroid measurement, J. Clin. Endocrinol., to be published.
8. WOOD, J. R., AND KINGSLAND, N.: Labeled sulfur uptake by thyroids of rats with low plasma thiocyanate levels, J. Biol. Chem. *185:* 833, 1950.